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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/457,931	12/08/1999	H. RALPH SNODGRASS	441472000100	8228

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	29

DATE MAILED: 04/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary

Application No.	Applicant(s)
09/457,931	H. Ralph Snodgrass
Examiner	**Art Unit**
Shin-Lin Chen	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 10, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *2-23 and 25-41* is/are pending in the application.

4a) Of the above, claim(s) *19, 20, and 34-41* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-8, 10-18, 21-23, and 25-33* is/are rejected.

7) ☒ Claim(s) *9* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Feb 10, 2003* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 2-10-03 has been entered. Claim 5 has been amended. Claims 2-23 and 25-41 are pending. Claims 2-18, 21-23 and 25-33 are under consideration.

Drawings

1. The corrected or substitute drawings were received on 2-10-03. These drawings are accepted.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 2-8, 10-18, 21-23 and 25-33 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann et al., 1997 (In Vitro Toxicology, Vol. 10, No. 1, p. 119-127) in view of Craig et al., 1996 (Biomarkers, Vol. 1, No. 2, p. 123-135) and Wobus et al., 1999 (US Patent 6,007,993) and is repeated for the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26).

Applicant argues that Spielmann teaches using mouse ES cells but not embryoid bodies (EB) and Figure 1 describes cell differentiation assay and does not describe the method of

determining the cytotoxicity of chemical composition by measuring EB cell death via MTT sytotoxicity test (amendment, p. 9). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26). Figure 1 of Spielmann reference teaches culturing ES cells to differentiate to EBs *in vitro*. Spielmann teaches ES cells develop into EBs after 3 days in suspension culture and to evaluate the toxicologic profile of test substances, an appropriate concentration of test chemicals was added into the ES cells and EBs (e.g., p. 121, right column). Table 1 shows cytotoxicity testing and inhibition of differentiation and "ID50 values obtained with chemicals of class 1-3 of embryotoxicity clearly show a ranking that correlates well with the embryotoxic potential of the test chemicals" (Table 1, p. 124, right column, second paragraph). Therefore, Spielmann does teach using EBs for testing cytotoxicity of test chemicals.

Applicant argues that Craig and Wobus do not remedy the limitations of Spielmann and there is no motivation to combine Spielmann with Wobus and Craig with reasonable expectation of success (amendment, p. 9, 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26) and the reasons set forth above. As discussed above, Spielmann does teach using EBs for testing cytotoxicity of test chemicals classes 1-3 as cited in the reference. On the other hand, Craig teaches using embryos of the topminnow, *Fundulus heteroclitus*, for reproductive toxicity screening by exposing the embryos to teratogenic concentrations of sodium valproate (VPA) or arsenic acid (arsenate) and evaluating the frequency and types of induced malformations. Craig correlates the teratogenic outcomes to

specific alterations in the expression of a panel of developmentally regulated genes and the genetic expression profiles revealed a number of genes whose expression levels were significantly altered by exposure to the test compounds.

Wobus teaches an *in vitro* test procedure for detecting chemically-induced embryotoxic/teratogenic effects based on differentiated pluripotent embryonic stem cells or embryonic germ cells obtained from primordial germ cells of the mouse or rat. A chemically-induced activation, repression or modulation of the tissue-specific genes which influence embryonic development is detected by using reporter gene constructs in the presence of teratogenic substances that act at specific times of the *in vitro* differentiation and subsequent differentiation. Wobus also teaches recording alterations in gene expression by monitoring protein expression after contacting an embryoid body with a chemical composition, and the change in expression is detected by a colorimetric label, e.g. X-Gal staining.

All of the cited references either teach using EBs for cytotoxicity testing of test chemicals or for detecting chemically-induced embryotoxic/teratogenic effects via gene expression or protein expression of a reporter, or teach using embryo of the topminnow, *Fundulus heteroclitus*, for reproductive toxicity screening by exposing the embryos to teratogenic substances. It would have been obvious for one of ordinary skill at the time of the invention to substitute the MTT cytotoxicity assay as taught by Spielmann with detection of gene expression as taught by Craig or detection of protein expression as taught by Wobus because it was known in the art to determine the effect of a chemical compound by detecting the alteration of gene expression or alteration of

protein expression. Therefore, the collective teachings of Spielmann, Craig, and Wobus would provide motivation to combine the cited references Spielmann, Craig, and Wobus to practice the claimed invention with reasonable expectation of success.

Applicant argues that Spielmann states that EST should be evaluated in other laboratories and more chemicals should be tested in the new test and one of ordinary skill would not be motivated to modify Spielmann's method (amendment, p. 10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26) and the reasons set forth above. Spielmann is just prudent in reporting and interpreting the scientific research result obtained as a scientist usually would do so in a scientific literature. It is very common that the results of a research literature need to be evaluated by other laboratories to confirm its validity or usefulness, and it does not mean that there should be no room to modify the method taught by Spielmann for improvement or other purposes. Further, it was known in the art to determine the effect of a chemical compound by detecting the alteration of gene expression or alteration of protein expression. Therefore, one ordinary skill in the art at the time the invention was made would have been motivated to generate a gene expression profile or protein expression profile of a teratogenic agent by using embryos or embryoid bodies as compared to a control having no treatment of said teratogenic agent as taught by Craig and Wobus, respectively, or to generate a library of gene expression or protein expression profiles of a test composition for typing or ranking toxicity of said test composition by using embryos or

embryoid bodies according to the collective teachings of Spielmann, Craig, and Wobus with reasonable expectation of success.

Applicant argues that human EBs recited in claims 10, 25, and chemical compositions recited in claims 11, 13, 16, 18, 23, 31 and 33 are not recited in the cited references (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26). The test chemicals cited by Spielmann includes aspirin, ascorbic acid, penicillin G, retinoic acid, saccharin and dexamethasone. Aspirin, penicillin, and ascorbic acid are therapeutic agents (claims 11, 16 and 31), and saccharin and dexamethasone are used in cosmetics (claims 13, 18 and 33). It was known in the art that human ES cell was first published in November, 1998, and was available at the time of the invention. Since Spielmann and Wobus teach using EBs for testing chemical toxicity, it would have been obvious for one of ordinary skill to use the EBs that are available, including EBs developed from human ES cells, at the time of the invention.

Applicant argues that the cited reference does not teach a method of ranking toxicity (amendment, p. 11). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 10-9-02 (Paper No. 26). Spielmann does teach a method of ranking toxicity of test chemicals. Table 1 shows cytotoxicity testing and inhibition of differentiation and "ID50 values obtained with chemicals of class 1-3 of embryotoxicity clearly show a ranking that correlates well with the embryotoxic potential of the test chemicals" (Table

1, p. 124, right column, second paragraph). Thus, claims 2-8, 10-18, 21-23 and 25-33 remain rejected under 35 U.S.C. 103(a).

Conclusion

4. Claims 2-8, 10-18, 21-23 and 25-33 are rejected. Claim 9 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

Shin-Lin Chen, Ph.D.